Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Anti-Infective Drugs Advisory Committee Meeting
January 22, 2015

Location: FDA White Oak Campus ,10903 New Hampshire Avenue, Building 31 Conference Center, The Great Room (Rm. 1503), Silver Spring, Maryland

Topic: The committee discussed new drug applications (NDAs) 207-500 and 207-501, isavuconazonium sulfate capsules and isavuconazonium sulfate for injection, sponsored by Astellas Pharma Global Development, Inc., respectively for the proposed indications of treatment of invasive aspergillosis and mucormycosis. These summary minutes for the January 22, 2015 meeting of the Anti-Infective Drugs Advisory Committee of the Food and Drug Administration were approved on March 5, 2015.

I certify that I attended the January 22, 2015 meeting of the Nonprescription Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Jennifer A. Shepherd, RPh
Designated Federal Officer, AIDAC

/s/
Dr. Thomas Moore, MD
Acting Chairperson, AIDAC

Summary Minutes of the Anti-Infective Drugs Advisory Committee Meeting
January 22, 2015

The following is the final report of the Anti-Infective Drugs Advisory Committee meeting held on January 22, 2015. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anti-Infective Drugs Products and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm424449.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Anti-Infective Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on January 22, 2015, at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Astellas Pharma Global Development, Inc. The meeting was called to order by Thomas Moore, MD (Acting Chairperson). The conflict of interest statement was read into the record by Jennifer Shepherd, RPh (Designated Federal Officer). There were approximately 100 people in attendance for the meeting. There were three Open Public Hearing speakers.

Issue: The committee discussed new drug applications (NDAs) 207-500 and 207-501, isavuconazonium sulfate capsules and isavuconazonium sulfate for injection, sponsored by Astellas Pharma Global Development, Inc., respectively for the proposed indications of treatment of invasive aspergillosis and mucormycosis.

Attendance:

Anti-Infective Drugs Advisory Committee Members Present (Voting): Ellen M. Andrews, PhD (Consumer Representative); Marc H. Scheetz, PharmD, MSc; Yu Shyr, PhD

Anti-Infective Drugs Advisory Committee Member Present (Non-Voting): Patrick Robinson, MD (Industry Representative)

Temporary Members (Voting): John Bennett, MD (via phone); Thomas A. Moore, MD, FACP, FIDSA (Acting Chairperson); Diane M. Cappelletty, PharmD; Paige E. Waterman, MD, FACP, FIDSA; Christopher T. Byrd, JD (Patient Representative); Tom Chiller, MD, MPHTM; Michael N. Neely, MD, MSc, FCP; Dean Follmann, PhD

FDA Participants (Non-Voting): Edward M. Cox, MD, MPH; Sumathi Nambiar, MD, MPH; Cheryl A. Dixon, PhD; Edward Weinstein, MD, PhD; John Alexander, MD, MPH

Open Public Hearing Speakers: Matthew J. Schueler, JD (Henry Schueler Foundation); Andrew Bartkowski; Thomas J. Walsh, MD (Henry Schueler Foundation)

The agenda was as follows:

Call to Order and Introduction of Committee	**Thomas A. Moore, MD, FACP, FIDSA** Acting Chairperson, AIDAC
Conflict of Interest Statement	**Jennifer Shepherd, RPh.** Designated Federal Officer, AIDAC
FDA Introductory Remarks	**John Alexander, MD, MPH** Clinical Team Leader Division of Anti-Infective Products (DAIP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Astellas Pharma Global Development, Inc.**
Compound Overview and Clinical Pharmacology	**Bernhardt Zeiher, MD, FACP, FCCP** Executive Vice President, Global Development and Therapeutic Area Head Immunology and Infectious Diseases Astellas Pharma Global Development, Inc.
Disease Background and Unmet Need	**Andrew Ullmann, MD** Professor of Infectious Diseases University of Wurzburg, Germany
Efficacy	**Rochelle Maher, MS** Senior Director, Global Development Project Leader, Infectious Diseases Astellas Pharma Global Development, Inc.
Safety	**Salim Mujais, MD** Vice President, Medical Head Infectious Disease/Immunology/Transplant Astellas Pharma Global Development, Inc.
Benefit-Risk	**Bernhardt Zeiher, MD, FACP, FCCP**
Clarifying Questions	
BREAK	

FDA PRESENTATIONS

Clinical Efficacy of Isavuconazonium for the Treatment of Invasive Aspergillosis	**Cheryl Dixon, PhD** Statistical Reviewer Division of Biometrics IV (DB IV) Office of Biostatistics (OB) Office of Translational Sciences (OTS) CDER, FDA
Clinical Efficacy of Isavuconazonium for the Treatment of Invasive Mucormycosis and Overview of Safety	**Edward Weinstein, MD, PhD** Medical Officer DAIP, OAP, OND, CDER, FDA

Clarifying Questions

LUNCH

Open Public Hearing

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **VOTE:** Has the applicant demonstrated substantial evidence of the safety and efficacy of isavuconazole for the proposed indication of treatment of invasive aspergillosis?

   a. If so, please provide any recommendations concerning labeling.

   b. If not, what additional studies/analyses are needed?

   Yes= 11 No= 0 Abstain= 0

   Committee Discussion: *The committee unanimously voted "Yes", agreeing that the applicant demonstrated substantial evidence of the safety and efficacy of isavuconazole for the proposed indication of treatment of invasive aspergillosis. With regard to labeling, the majority of the committee shared the opinion that the labeling should include warnings and information for use in pregnant and/or breastfeeding women, children under 18 years old, patients with short QT syndrome, patients of non-white descent (specifically of Asian descent) and any need for drug monitoring. The committee also noted that the label should include information that addresses the possibility for particulate matter to develop, and that the vial should not be shaken during reconstitution and the bag should not be shaken after*

reconstitution. In addition, one member noted that the label should include information that the drug will dissolve in blood/plasma. Several committee members mentioned the need for therapeutic drug monitoring. Additionally, several members agreed that there is a need for more study in the effects of the drug on the QT interval, drug interactions, and the need for drug monitoring. One member expressed the need for study in patients younger than 18 years old. Please see the transcript for details of the committee discussion.

2. **VOTE:** Has the applicant demonstrated substantial evidence of the safety and efficacy of isavuconazole for the proposed indication of treatment of mucormycosis?

   a. If so, please provide any recommendations concerning labeling.

   b. If not, what additional studies/analyses are needed?

   Yes=8 No= 2 Abstain= 1

   Committee Discussion: *The majority of the committee voted "Yes", indicating that the applicant demonstrated substantial evidence of the safety and efficacy of isavuconazole for the proposed indication of treatment of mucormycosis. However, the committee was hesitant to move forward with the recommendation for approval for the main reason that the data that were presented for approval depend on historical controls and there was no direct comparison with AmphotericinB. Nevertheless, it was noted that, given the difficulty in gathering data for such a rare condition, the data do seem to suggest effectiveness. The majority of the committee stated that the unmet need for this rare disease influenced their decision to vote in favor of approval. If approved for treatment of mucormycosis, one member noted that it is critical that the FDA require the labeling to include the fact that isavuconazonium was not compared to AmphotericinB in any head-to-head studies, and that historical controls were used to support approval as it will be difficult for clinicians to determine what would be first-line therapy. One member also noted that the FDA should require the sponsor to study the drug in patients with neutropenia and fever as the drug, if approved, would most likely be used in that patient population. Several committee members mentioned that there is a critical need for Phase IV studies to be conducted. Two committee members voted "No" and one of those members expressed the concern that if the Agency sets the bar this low for a "secondary" approval, it will be flooded with "primary" approvals for drugs that will reach the market that shouldn't. The other member who voted "No" stated that a better comparison of death rate with relation to AmphotericinB is needed prior to approval. The abstaining member cited the ambivalence of the data but noted that clinicians should have the drug available as a treatment option. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at 2:18 pm.